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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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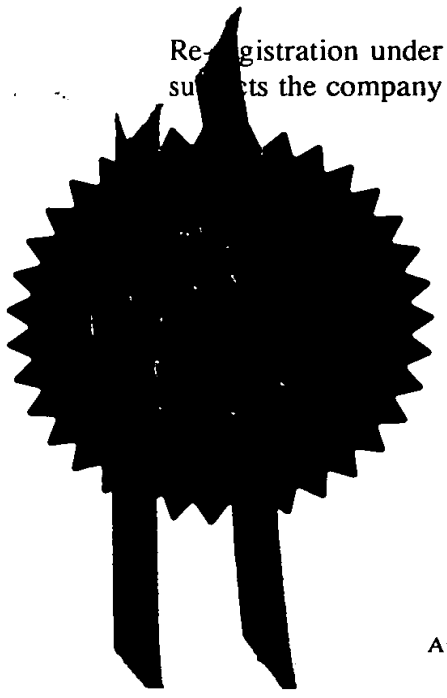

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Dated 17 August 1999

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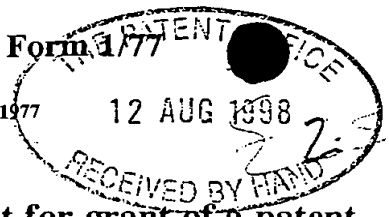

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1.	**Your reference**	33.67951
2.	**Patent application number** *(The Patent Office will fill in this part)*	**9817573.0**
3.	**Full name, address and postcode of the or of each applicant** *(underline all surnames)*	EDKO TRADING AND REPRESENTATION COMPANY LIMITED P O Box 228 Sisli, 80233 Istanbul, Turkey
	Patents ADP number *(if you know it)*	
	If the applicant is a corporate body, give country/state of incorporation	Turkey
4.	**Title of the invention**	Pharmaceutical Compositions
5.	**Name of your agent** *(if you have one)*	Frank B. Dehn & Co.
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	179 Queen Victoria Street London EC4V 4EL
	Patents ADP number *(if you know it)*	166001

6.	**If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and** *(if you know it)* **the or each application number**	**Country**	**Priority application number** *(if you know it)*	**Date of filing** *(day / month / year)*
7.	**If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application**	**Number of earlier application**		**Date of filing** *(day / month / year)*
8.	**Is a statement of inventorship and of right to grant of a patent required in support of this request?** *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	Yes		

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Continuation sheets of this form	
Description	9 / R
Claim(s)	
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10. **If you are also filing any of the following, state how many against each item.**

Priority documents	
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application.**

Signature **Date** 12 August 1998

Frank B. Dehn & Co.

12. **Name and daytime telephone number of person to contact in the United Kingdom**

H.J. Skailes
0171 206 0600

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PHARMACEUTICAL COMPOSITIONS

This invention concerns formulations of nimesulide for topical application.

Nimesulide is a nonsteroidal anti-inflammatory agent (NSAID) which has poor solubility. It has been formulated at various concentrations as a suspension in vehicles containing pharmaceutically acceptable excipients. These vehicles typically consist of aqueous gels containing about 1% nimesulide. The drug in suspension has limited therapeutic activity as its percutaneous absorption is impaired by the difficulty of releasing free drug molecules from the suspenzoid. Solubilized nimesulide offers the advantage of immediate availability of free drug molecules to the receptor site, and clear gels of nimesulide have been prepared using different pharmaceutical solvents. However, when the finished gel products are applied topically, they produce an unpleasant yellowish stain on the skin or clothing.

The objective of the invention is to provide nimesulide compositions which are both therapeutically effective and non-staining or substantially non-staining when applied topically. We have found that this desirable combination of properties can be achieved in composition, preferably a gel, in which a solution of

nimesulide is entrapped in a liquid crystal system, in particular in the lipid bilayers of the cubic phase of a liquid crystal former such as glyceryl monoolein. The compositions enable the nimesulide to penetrate the skin rapidly. The nimesulide is then released in the skin slowly as compared to conventional formulations, thus providing a long-acting or sustained release effect which is advantageous in the treatment of the conditions for which nimesulide is used.

The invention thus provides a formulation of nimesulide for topical application to the skin which contains an aqueous solution of nimesulide in a liquid crystal system and is in the form of a gel or a solution. The composition is preferably in the form of a gel.

The nimesulide may generally be present in this composition in amount of 0.1 - 3.0% or up to 5% by weight, usually and preferably about 1% by weight.

The solvent for the nimesulide should be pharmaceutically acceptable and may for example be or a C_{1-6} alcohol, N-methylpyrrolidone, glycol or ether glycol (e.g. a C_{2-6} compound such as propylene glycol, 1,3-butylene glycol, dipropylene glycol or diethylene glycol), ether (e.g. a C_{2-6} ether such as diethyl ether or diethylene glycol monoethyl ether (DGME)), or a C_{8-22} glyceride or ethoxylated glyceride (e.g. capric, caprylic, arachinoic and behanoic glycerides and ethoxylated derivatives thereof, particularly caprylic/

capric triglycerides or derivatives containing for example 6 polyoxyethylene units). Mixtures of these solvents can also be used. A solvent system containing DGME and a C_{1-6} alcohol such as ethanol is preferably used, with the DGME generally in an amount of 35 - 45% by weight and the alcohol in an amount of 25 - 35% by weight of the composition.

Water is also included in the solvent system, generally in amount of 5 - 15% by weight, and this facilitates the formation of the liquid crystal structure required.

The liquid crystal forming material is preferably glyceryl monoolein (or monooleate), which is available commercially as a distilled monoglyceride mixture with a high monoolein content (for example GMOrphic, from Eastman Chemicals, USA). This forms a cubic liquid crystal phase having lipid bilayers of the monoolein, and these bilayers have channels which surround or trap the nimesulide solution. It is believed that the molecular structure of nimesulide enables it to become aligned and trapped within the bilayers, and when the water and volatile solvents evaporate after application, the bilayers then penetrate into the skin. This penetration takes place rapidly, before release of the nimesulide, and this prevents the staining of the skin by the nimesulide from occurring. The nimesulide is then released comparatively slowly from the liquid crystal structure, probably as a result of contact with

natural skin constituents.

Other liquid crystal formers which provide a similar liquid crystal structure may also be used, for example cholesterol or a derivative (such as cholesterol oleate) or lecithin or a derivative such as an oleate. The liquid crystal former can generally be used in amounts of 10 - 45% by weight of the composition, with amounts of 10 - 20% by weight being preferred in the case of glyceryl monoolein.

The composition also preferably includes a gelling agent such as carboxypolymethylene (carbomer, e.g. Carbopol) or a fumed silicon dioxide, for example Cab-O-Sil. Although gelling agents are not required for the formation of liquid crystals, they may assist in maintaining the long term cubic phase structure integrity and can influence the shelf life stability of a finished product. These agents can additionally offer greater flexibility to the formulator in designing finished products with varied consistencies and levels of thickness. Generally, these agents can be used in amounts of 0.1 - 10% by weight of the composition.

Other ingredients can also be included in the formulation, for example capsicum oleoresin, capsaicin, nicotinates, camphor, menthol or turpentine oil. Capsaicin is preferred for compatibility with the formation of stable liquid crystal systems and can be included for example in amounts of 0.001 to 0.25%.

The compositions may be prepared by first dissolving the nimesulide in the solvent(s) and water and then mixing the solution at 30 - 90°C with a liquid crystal former such as glyceryl monoolein which has been heated to 35 - 55°C, followed by agitation and cooling to room temperature. A gelling agent may then be mixed in, either on its own or as an alcoholic gel. When a further active ingredient such as a rubefacient is included, this can be mixed in as a final step.

The nimesulide compositions can be used for a variety of indications characterised by pain and inflammation, or stiffness. Such indications are: osteoarthritis of superficial joints, such as the knee, ankle, wrist and elbow; rheumatism, acute musculoskeletal injuries and/or bruising; muscular cramp; strains; sprains; periarthritis; epicondylitis; tendinitis; bursitis; tenosynovitis; tennis elbow; back strain; lumbago; sciatica; neuralgia; and fibrositis. The compositions are applied topically to the skin, which should be clean and is preferably cleansed before use. This allows the composition to penetrate the skin without disruption of the cubic phase, thus avoiding staining, and prevents surface materials such as salt or grime from complexing with any gellant present and coagulating the composition. Cleaning also provides a better surface for penetration by the composition.

The following examples illustrate the invention.

Example 1

Diethylene glycol monoethyl ether	42.5 % w/w
SD alcohol (ethanol)	30 % w/w
Water	10 % w/w
Nimesulide	1 % w/w
Glyceryl monoolein	16.5 % w/w

The nimesulide was dissolved in the solvents and water, and the solution heated to 45°C. This heated solution is added to the glyceryl monoolein which had been heated to 45°C. The mixture was agitated and cooled to room temperature to give a clear solution.

Example 2

Diethylene glycol monoethyl ether (DGME)	40 % w/w
SD alcohol (ethanol)	30 % w/w
Water	10 % w/w
Carbomer	2.5 % w.w
Nimesulide	1 % w/w
Glyceryl monoolein	16.5 % w/w

The nimesulide was dissolved in the solvents and water, and the solution heated to 45°C. This heated solution was added to the glyceryl monoolein which had been heated to 45°C. The mixture was agitated and cooled to room temperature. The gelling agent (carbomer) was then mixed in to the desired consistency

to provide a clear gel.

A variation of this procedure is first to prepare separately a gel of alcohol and the gelling agent by thorough mixing. A solution of the nimesulide in the water and DGME is prepared separately by adding the nimesulide slowly to the solvent mixture at 48-50°C. The glyceryl monoolein heated to 48-50°C is added slowly to the nimesulide solution with mixing to give a clear composition and cooled to room temperature. The alcoholic gel is then slowly mixed in to give a uniform gel.

Example 3

Diethylene glycol monoethyl ether	40 % w/w
SD alcohol (ethanol)	30 % w/w
Water	10 % w/w
Fumed silicon dioxide	7.0 % w/w
Nimesulide	1 % w/w
Glyceryl monoolein	16.5 % w/w

The nimesulide was dissolved in the solvents and water, and the solution heated to 45°C. This heated solution was added to the glyceryl monoolein which had been heated to 45°C. The mixture was agitated and cooled to room temperature. The gelling agent (silicon dioxide) was then mixed in to the desired consistency to provide a clear gel.

A variation of this procedure is to prepare separately a gel of alcohol and the gelling agent and to add this to the rest of the formulation at room temperature.

Example 4

Diethylene glycol monoethyl ether	40 % w/w
SD alcohol	30 % w/w
Water	10 % w/w
Carbomer	2.5 % w/w
Nimesulide	1.0 % w/w
Glyceryl monoolein	16.475 % w/w
Capsaicin	0.025 w/w

A clear gel was prepared as described in Example 2 and the capsaicin then added in a final step and mixed in until dissolved and homogenous.

The formulations prepared in the above examples have been tested and found to be therapeutically effective when applied topically to human skin. They did not produce any perceptible stain on the skin as determined by visual observation. Photomicrographs of the formulations at 40X showed a clear transparent medium and no nimesulide crystals were observed, indicating that the nimesulide is only present in solution. This is in contrast to photomicrographs of nimesulide dispersions, which clearly show nimesulide particles distributed throughout the composition. The

compositions were also found to be storage stable, and for example it was possible to keep them at 40°C for 60 days or more.